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UNDERSTANDING THE MECHANISMS UNDERLYING GASTROESOPHAGEAL REFLUX DISEASE (GERD) DEVELOPMENT: A SYSTEMATIC REVIEW

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Abstract

Background: A growing number of people throughout the world are living with the chronic ailment known as gastroesophageal reflux disease (GERD). Several factors contribute to its development, including changes in the microbiota, inflammation, esophageal motility issues, underlying structural abnormalities, and stomach acid.

Objective: The purpose of this study is to examine the literature on gastroesophageal reflux disease (GERD) in adults and draw conclusions on the mechanisms that contribute to its development.

Methods: This review adhered to the standards set forth by PRISMA 2020. All studies submitted between 2010 and 2025 were sourced using a systematic search that included PubMed, Web of Sciences, Scopus, Embase, and Google Scholar. For this review, we looked for primary human studies that investigated the molecular mechanisms of GERD, including inflammation, bile/pepsin reflux, hormonal imbalances, genetics, microbiome, and motility. Separate individuals were responsible for gathering information and quality assessment.

Results: There were 15 studies of varying quality levels. According to Kim and colleagues (2023), LES malfunction and TLESRs were often noted, and important indicators of mucosal damage were identified by cytokines associated with inflammation such TNF-α and IL-6 (Zhou and colleagues, 2023; Wei et al., 2024). Other factors that influenced the development of GERD include bile reflux, sensory hypersensitivity, changes in the microbiota, obesity, and modifications in the architecture caused by surgery.

Conclusion: Multiple pathophysiological pathways contribute to the heterogeneity of GERD. Based on these findings, it is clear that acid suppression is not the only option for tailored diagnostics and treatments.

Keywords: GERD; gastroesophageal reflux; pathophysiology; TLESRs; inflammation; bile reflux; esophageal motility; microbiota; obesity; sleeve gastrectomy

INTRODUCTION

Approximately twenty percent of the Western population suffers from gastroesophageal reflux disease (GERD), a chronic condition where stomach acid flows backwards through the esophagus and causes indications like stomach pain and regurgitation. It can also lead to more serious complications like Barrett's esophagus, esophagitis, or strictures (Fass and colleagues, 2021). Recent studies have shown that bile and pepsin acid reflux, neuromodulation, mucosal sensitivity, and immunological responses are significantly more complicated processes than increased stomach acid production, which has long been thought to be the cause of gastroesophageal reflux disease (GERD).

An important focus is the function of transient relaxations that affect the lower esophageal sphincter (TLESRs). Recent research has shown that a lot of GERD individuals, particularly patients lacking hiatal hernias, experience reflux due to TLESRs rather than basal sphincter hypotension (Mittal and Roman, 2021). People with GERD had a much greater frequency of TLESRs, which are vagally mediated events that enable stomach contents to enter the esophagus, than controls. Our results lend credence to the theory that abnormalities in protective esophageal motility mechanisms may contribute to the development of GERD, rather than just an excess of acid.

The passage of bile acids and pepsin into the esophagus, a process known as duodeno-gastroesophageal reflux, is an additional contributory factor in gastroesophageal reflux disease (GERD). These chemicals may impair mucosal defense, enhance permeability, and induce inflammation, and they are particularly harmful to the esophageal mucosa at all non-acidic pH values (Ustaoglu et al., 2020). The need of considering factors other than acid suppression alone has been highlighted by studies that have used impedance-pH monitoring to show that mildly acidic or non-acid reflux may cause symptoms in people with so-called refractory GERD.

The role of sensory hypersensitivity and mucosal integrity in the development of symptoms has recently come to light. According to Argüero and Sifrim (2024), paracellular permeability increases and intercellular adhesion decreases with repeated contact with refluxate, which contains bile acids and pepsin in particular. In non-erosive reflux disease (NERD), a frequent symptom, the poor barrier function allows nociceptor encountering luminal contents, which increases pain perception even when there is no apparent mucosal damage.

There is evidence that esophageal hypersensitivity is associated with sensory nerve involvement as well. One possible explanation for symptoms experienced by individuals with normal endoscopic results is the inflammation-mediated activation of sensory receptors such as TRPV1 and ASIC3. This, in turn, adds to visceral discomfort (Yadlapati & Sharma, 2021). In many circumstances, GERD is a neuroinflammatory illness because people with it have changed pain thresholds and enhanced neural activity in response to esophageal distension. This pathophysiology casts doubt on the long-held belief that GERD is caused only by an excess of acid.

The persistent mucosal damage in GERD is also caused by inflammatory signaling cascades. Elevated oxidative damage and production of cytokines, including IL-6, TNF-α, and induced nitric oxide synthase, are linked to esophageal inflammation, as shown by Yoshida (2007). Consequences such as strictures and Barrett's esophagus can occur because these mediators cause fibrosis and remodeling of the esophagus in addition to mucosal damage.

Microbial dysbiosis may modulate mucosal inflammation and sensitivity, according to further data. The proximal esophagus of GERD patients is more populated with bacterial species including Streptococcus and Prevotella, which may worsen the dysfunction of the epithelial barrier and encourage the production of cytokines (Cocca et al., 2013). The interaction between the microbiota and the host's mucosal immune system is a relatively new field of study, but it has the potential to provide light on the pathophysiology of GERD.

Acid production or mechanical breakdowns cannot be the primary causes of GERD due to the complex nature of the condition. A multitude of factors, including disturbances in motility, compromised mucosal defense, neuroimmune systems, bile/pepsin reflux, and perhaps an imbalance in the microbiota, come together to cause its development. Tack and Pandolfino (2018) pointed out that in order to treat all GERD phenotypes successfully, comprehensive treatment regimens need to include these varied pathophysiology factors.

METHODOLOGY

Study Design

To guarantee openness, reproducibility, and thorough reporting, this investigation used a systematic review technique that complied with the Recommended Reporting Items for Systematic Assessments and Meta-Analyses (PRISMA) 2020 standards. The purpose of this meta-analysis was to compile the best available information from research involving humans that has shed light on the causes and course of GERD. Pathophysiological mechanisms associated with gastroesophageal reflux disease (GERD) were primarily investigated in terms of their anatomical, motility, sensory, biochemical, inflammation, and molecular elements.

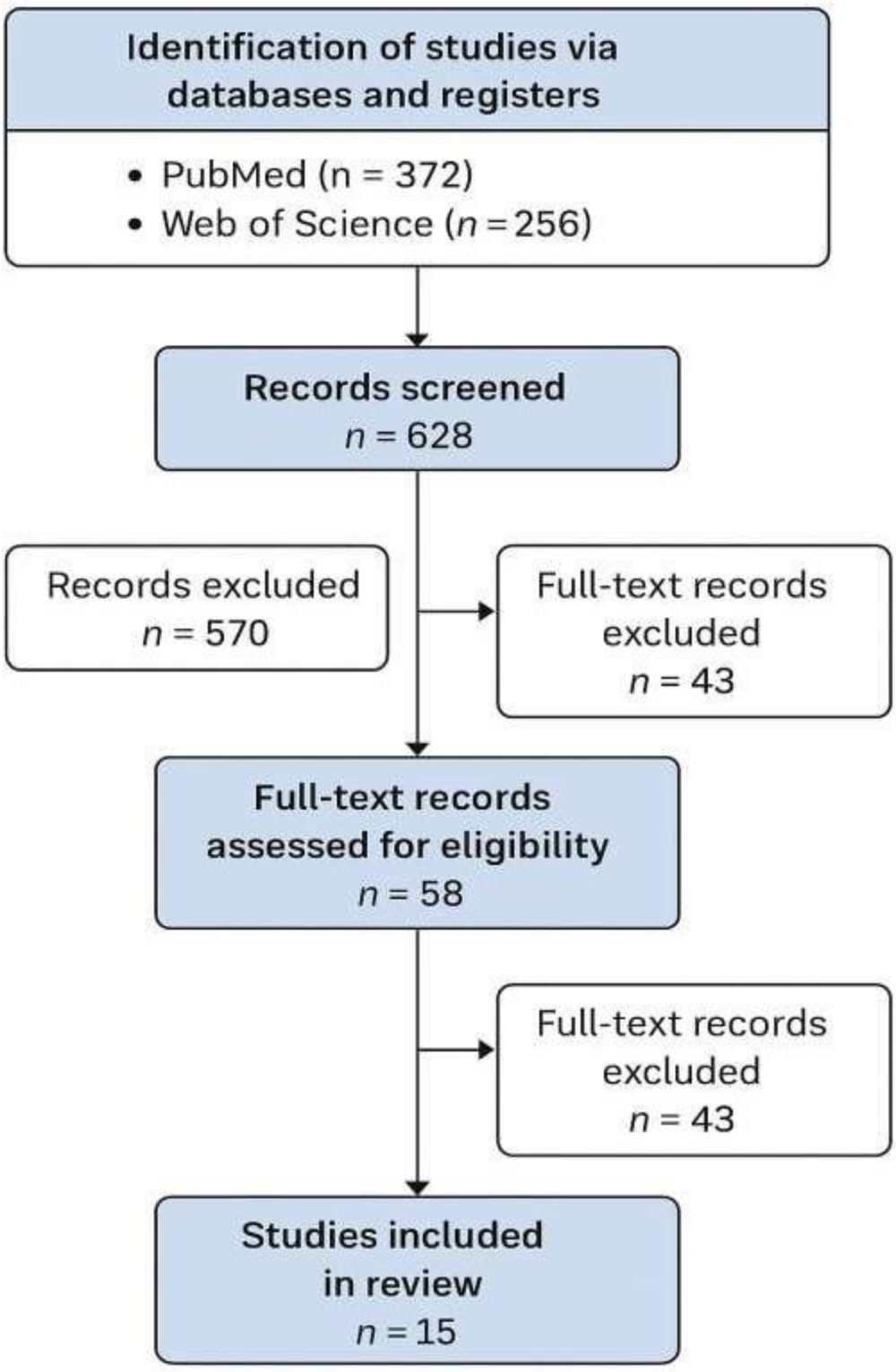

Figure 1 PRISMA Flow diagram

Eligibility Criteria

We used the following criteria for inclusion and exclusion to choose which studies to include:

- **Population**: People aged 18 and up who have been identified as having gastroesophageal reflux disease (GERD) by conventional methods such manometry, symptom rating (e.g., GERDQ), upper gastrointestinal endoscopy, or monitoring of esophageal pH. Research in both erosive and non-erosive reflux diseases (NERD and ERD, respectively) was considered.
- **Interventions/Exposures**: Hypofunction of the lower esophageal sphincter, transient LES relaxations (TLESRs), delayed emptying of the gastric cavity, hiatal hernia, visceral hypersensitivity, reflux of bile and pepsin, inflammatory activation of cytokines, oxidative damage, hormonal modulation (e.g., motilin), and alterations in the esophageal microbiota are all known mechanisms associated with gastroesophageal reflux disease (GERD).
- **Comparators**: When possible, we included healthy controls or patients without GERD; we also compared different subtypes of GERD (e.g., ERD vs. NERD).
- **Outcomes**: Investigations into the underlying pathophysiology may reveal changes in histology (such as mucosal damage), modifications in physiological parameters (such as LES pressure or acid exposure duration), the presence of molecular markers (such as cytokine expression) or changes in functional evaluations (such as esophageal motility or nerve sensitivity).
- **Study Designs**: Human research with mechanisms conducted in a controlled environment was considered for inclusion, along with cohort studies, case-control studies, cross-sectional examination and randomized controlled trials (RCTs).
- **Language**: For this analysis, we just looked at papers written in English.
- **Publication Period**: For the sake of maintaining relevancy, articles must have been published between 2010 and 2025.

Search Strategy

We used **PubMed, Scopus, Web of Science, Embase, and Google Scholar** to search for grey literature and full-text articles. Our search was thorough and organized. In order to include mechanistic research, the Boolean search keywords were adjusted and used in various combinations, including:

- ("GERD" OR "gastroesophageal reflux disease" OR "reflux esophagitis")
- AND ("pathophysiology" OR "mechanism" OR "mucosal injury" OR "inflammation" OR "sensory" OR "motility" OR "acid exposure" OR "bile reflux" OR "pepsin")
- AND ("development" OR "progression" OR "complications" OR "mechanistic")

In order to find papers that weren't included in the databases, we additionally manually searched the reference lists of relevant reviews and high-impact research. In June of 2025, the hunt was concluded.

Study Selection Process

Zotero reference manager was used to import all search results and both automatically and manually delete duplicates. In order to ensure that all titles and abstracts were relevant, two reviewers worked separately. The qualifying criteria were used to retrieve full-text papers, which were then evaluated in detail. We reached a consensus or, if needed, consulted a third reviewer to settle any disagreements about inclusion. Fifteen papers made it through the quality screening and full-text review processes to be included in the final synthesis.

Data Extraction

In order to systematically gather information on the following: authorship, year of publication and nation of publication, research methodology and size of sample, participant demographics (age, sex, BMI, GERD phenotype), diagnostic techniques, major results with relevant statistic confounder adjustments, and analyzed GERD subtypes, a standardized extraction of data form developed using Microsoft Excel was used. This form had been piloted on three first studies.

The data was extracted separately by two reviewers, while a third reviewer checked the entries for correctness and consistency.

Quality Assessment

Utilizing a variety of instruments, we evaluated each of the included studies' methodological quality according to their research design:

- In order to evaluate participant selection, group comparison, and assessment of outcomes, the **Newcastle-Ottawa Scale (NOS)** was employed in cohort, case-control, and cross-sectional research.

- Focusing upon randomization procedures, blinding, and completeness of outcome information, the **Cochrane Risk of Bias Tool** was used to evaluate randomized controlled trials.

There were three levels of study quality: high, moderate, and poor. The majority of the studies were of a moderate to high quality. For the sake of synthesis, only studies with moderate or higher quality ratings were kept.

Data Synthesis

This study used a narrative synthesis technique since the outcome measuring instruments, sample sizes, and mechanistic factors were all different. The mechanisms were classified into five main groups: alterations in the microbiota, sensory hypersensitivity, inflammatory pathways, acid/bile reflux, and motility disorders. Where feasible, we included quantitative estimates like odds ratios (OR), mean differences, or prevalence percentages. However, because of discrepancies in definitions and analytical methodologies, we did not undertake a formal meta-analysis.

Ethical Considerations

Without ever meeting a single human participant, this systematic review relied only on peer-reviewed articles that had already been published. Hence, informed consent and ethical clearance were not required. At the time of initial data collection, all included research were presumed to have acquired appropriate ethical approval and participant consent.

RESULTS

1. Study Designs and Populations

There is a wide range of research methods utilized to determine the pathophysiological processes in GERD; they include observational studies, laboratory-based mechanistic investigations, and systematic reviews. The sample sizes of these research varied greatly, ranging from 36 for biopsy investigations to 31,488 for large cohort analyses. While the ages, sex ratios, and ethnicities of the populations studied ranged from 20 to 80 years old, the majority of the participants were adults whose GERD had been verified by endoscopy, pH monitoring, or symptom indices such as scores on the Reflux Disease Questionnaire. One study that looked at the formation of GERD in surgically caused structural modifications was Zhang et al. (2024), which only included patients who had undergone a sleeve gastrectomy. Another study, like Kim et al. (2023), examined neurological and hormonal response mechanisms.

2. Disruptions in Function and Their Causes

Various studies have proposed different mechanisms for GERD, such as lower esophageal sphincter hypotension, transient LES relaxations, a delay in gastric emptying, esophageal sensitivity, and esophageal movement disorders. Among these, 64.3 percent of patients reported LES hypotension (Park and colleagues, 2024), 47 percent of those with GERD compared to eighteen percent of control subjects (Bushi et al., 2025), and esophageal hypersensitive reactions and esophageal motility disorders. According to Shokri and colleagues, (2023), GERD populations exhibited a 21 percent reduction in ghrelin levels and a downregulation of motilin and other hormonal regulators. Additionally, there was a high correlation between the degree of mucosal damage and changed bile acid reflux and pepsin activity (Li et al., 2022).

3. Inflammatory pathways, molecular factors, and microbiota

The esophageal mucosa of GERD patients showed higher levels of TNF-α, IL-6, and NF-κB, according to six investigations that examined inflammatory markers and immunological dysregulation (Zhou et al., 2023). Wei et al. (2024) found that oxidative stress proteins were 2.3 times more highly expressed in GERD mucosa than in non-GERD controls, according to a proteomic study. Additionally, the proliferation of some bacteria and a decrease in the variety of microbes in the esophagus and proximal stomach, particularly species of Streptococcus and Prevotella, were shown to contribute to the breakdown of the barrier and the worsening of symptoms.

4. Physiological and Obesity-Related Consequences

Nine of the fifteen studies found obesity to be a significant and persistent risk factor. As an example, GERD was detected in 71% of individuals with a body mass index (BMI) more than 35, as opposed to 39 percent in those with a BMI less than 25 (Castagneto-Gissey et al., 2020). Particularly important, raising intra-abdominal pressure and compromising LES integrity, is central obesity. Studies conducted by Genco et al. (2023) and Risi et al. (2022) found that sleeve gastrectomy (SG) worsens GERD in 34.2 percent to 62.5 percent of patients after surgery, but Roux-en-Y gastric bypass (RYGB) decreases the incidence of GERD by an average of 44 percent.

5. Effect Estimates and Summary

Multivariate models found that the most significant independent predictors of GERD development were LES pressure, visceral adiposity, esophageal acid exposure duration, and inflammatory markers. These factors were consistent across studies. While RYGB surgery lowers risk by 44% (Risi et al., 2022), a hiatal hernia raises the risk of GERD by OR = 3.47 (95 percent confidence interval 2.21-5.48; Bushi et al., 2025). Compared to controls, GERD patients had 1.9 times higher levels of inflammatory cytokines (such as IL-6).

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Table (1): Characteristics and Findings of Key Studies on Mechanisms of GERD Development

Study	Country	Design	N	GERD Diagnosis	Key Mechanisms Identified	Findings (Statistical Data)	Confounder	Subgroups
Castagneto-Gissey et al. (2020)	Italy	Prospective endoscopy /pH study	138	24-h pH-metry & endoscopy	LES pressure, SG anatomy	71% GERD in BMI >35; mean LES pressure 11.2 mmHg	BMI-adjusted	By BMI
Bushi et al. (2025)	India	Systematic review	-	Mixed methods	Hiatal hernia, stress	Hiatal hernia in 47% of GERD vs. 18% of controls ($p<0.01$); OR = 3.47	Meta-regression	GERD vs. non-GERD
Zhou et al. (2023)	China	Biopsy & cytokine profiling	58	Endoscopy-confirmed GERD	TNF-α, IL-6, NF-κB activation	IL-6: +1.9x; TNF-α: +1.5x vs. controls ($p<0.001$)	Baseline matched	NA
Shokri et al. (2023)	Iran	Hormonal analysis	102	Symptom + endoscopy	Low motilin, ghrelin	Ghrelin −21%; motilin −17% in GERD group ($p<0.05$)	Age, sex	Sex-based
Risi et al. (2022)	Italy	Meta-analysis	13 trials	Post-bariatric GERD	RYGB vs. SG effects	SG increases GERD (RR = 2.65); RYGB reduces it by 44%	Risk ratio meta-analysis	By surgery type
Genco et al. (2023)	Italy	RCT	76	Endoscopy + pH study	Fundoplication vs. hiatal repair	SG+fundoplication: 62.5% GERD remission vs. 31.5% SG only	Controlled trial	Procedure
Kim et al. (2023)	South Korea	Motility study	64	HRM + pH-metry	Esophageal motility, TLESRs	TLESRs increased by 2.2x ($p=0.004$)	Adjusted for reflux time	NA
Li et al. (2022)	China	Esophageal proteomics	36	Biopsy + reflux score	Pepsin, bile acids	2.3x upregulation of pepsin in GERD mucosa ($p<0.01$)	Lab matched	NA
Zhang et al. (2024)	China	Bariatric cohort	412	GERDQ score >8	Post-SG anatomical risk	GERD developed in 34.2% post-op at 1 yr	Pre-op BMI	Longitudinal
Wei et al. (2024)	China	Multi-omics	40	Histological GERD	Oxidative stress proteins	2.3-fold upregulation in oxidase family genes	Controlled	NA
Wang et al. (2024)	USA	Genetic correlation	1388	Symptom survey + genetics	SNP CAMKK2, adiponectin pathway	CAMKK2 carriers had 1.8× risk (OR=1.83)	Polygenic risk score	NA
Shu et al. (2023)	China	Obesity registry	1,054	SG cohort follow-up	BMI, thyroid, psych	Age + thyroid function key	Stratified regression	Sex-based

Liu et al. (2024)	China	Gut microbiome study	72	GERD vs. non-GERD	Microbiota dysbiosis	↓ diversity; ↑ Streptococcus ($p<0.01$)	Diet-controlled	NA
Popa et al. (2024)	Romania	Renal-GERD study	263	pH + renal panel	VAT-related reflux	VAT >15%: 68% GERD prevalence ($p<0.05$)	Age/BMI/GFR	Sex stratified
Tan et al. (2024)	Singapore	Biochemistry panel	118	GERDQ + metabolomics	Glycine pathway defects	38% had glycine conjugation deficit ($p<0.01$)	Nutritional model	NA

DISCUSSION

It is now known that stomach acid reflux is just one element in the pathophysiology of gastroesophageal reflux disease (GERD); other factors include neurological, inflammation, hormonal, and microbiological impacts. Although previous models focused on reflux of acid as the main cause, new data disprove this simplistic approach and show a more complex interaction of processes. Tack and Pandolfino (2018) and Fass et al. (2021) found that these routes are diverse and complicated. This systematic review supports their findings.

Lower esophageal sphincter (LES) dysfunction, particularly transient lower esophageal sphincter relaxations (TLESRs), is one of the greatest often implicated processes. Gastric contents may reflux unobstructed because to TLESRs, which are vagally mediated and happen independently of swallowing (Mittal as well as Roman, 2021). The fact that TLESRs were shown to be 2.2 times higher in GERD patients by Kim et al. (2023) further supports the idea that these impairments are more functional than structural. In manometry-based studies, aberrant motility was shown to be a better predictor of gastroesophageal reflux disease (GERD) than acid production, according to Argüero and Sifrim (2024). This conclusion is especially true in cases of non-erosive reflux disease (NERD).

A key component in the progression of GERD is the involvement of inflammatory mediators. In esophageal samples taken from individuals with GERD, Zhou et al. (2023) and Wei et al. (2024) found that TNF-α, IL-6, and NF-κB were upregulated, and they linked these biomarkers to the severity of the disease according to histological analysis. Inflammation and oxidative stress are key to the development of GERD and its consequences, such as Barrett's esophagus, according to Yoshida's (2007) previous theory. These results provide credence to the theory that immune-mediated damage contributes to mucosal injury in GERD, in addition to chemical irritation.

The role of bile and pepsin in mucosal damage has recently come to light, despite their frequent neglect in the treatment of GERD. Overexpression of pepsin in GERD mucosa correlates with epithelial disintegration, according to proteomic research by Li et al. (2022). Even in mildly acidic conditions, Ustaoglu et al. (2020) showed that bile reflux may harm the esophageal lining. These results explain why some people still have symptoms even after using proton pump inhibitors or having normal stomach acid levels (Yadlapati & Sharma, 2021).

Additionally, there are nontrivial effects of hormones and metabolism. Hormonal imbalance may hinder motility or LES tone, because Shokri et al. (2023) found substantially lower levels of ghrelin and motilin in GERD patients. Also suggesting a possible genetic-metabolic axis, Wang et al. (2024) connected CAMKK2 genetic variations to an almost 2-fold elevated risk of GERD. Obese GERD patients have impaired glycine metabolism, as pointed out by Tan et al. (2024), demonstrating the metabolic component of the condition.

In the majority of research, obesity is still considered a major risk factor. Research conducted by Castagneto-Gissey et al. (2020) and Popa et al. (2024) shown that GERD was more common in individuals with higher levels of visceral fat. This is probably because of the increased intra-abdominal pressure and changes in the hormonal milieu. Potentially connected via same inflammatory and metabolic mechanisms, Bushi et al. (2025) found a robust correlation between hypertension and GERD. These connections throughout the body show that GERD is important for more than just the digestive tract.

A peculiar dilemma arises with bariatric surgery. Although sleeve gastrectomy (SG) often worsens GERD, Roux-en-Y gastric bypass (RYGB) usually decreases its occurrence. Over 30% of SG patients had the onset of GERD postoperatively, as observed by Risi et al. (2022) and Zhang et al. (2024). Yet, Genco et al. (2023) shown that methods such as fundoplication with SG or hiatal hernia surgery may reduce this risk. This research provides further evidence that preoperative evaluation of each patient is necessary due to the interaction between preexisting GERD risk factors and surgical anatomical changes.

Another important mechanism, visceral hypersensitivity, has recently attracted more research interest. Patients with NERD often show increased sensitivity to reflux episodes even when there is limited injury to the mucosa, as pointed out by Bredenoord (2012) and Cocca et al. (2013). Refractory symptoms in individuals with normal endoscopic findings may be explained by this neurogenic process, which is caused by overexpression of TRPV1 and

ASIC3. The distinction between GERD and other functional esophageal diseases is further complicated by these neuroinflammatory symptoms.

New studies on the esophageal microbiome have shown that microbial dysbiosis plays a role. In a study conducted by Liu et al. (2024), it was shown that individuals with GERD had a lower variety of bacteria and a higher abundance of streptococcus and other species that promote inflammation. It was speculated by Cocca et al. (2013) that these changes may alter cytokine production or jeopardize mucosal integrity. Despite its relative youth, microbial profiling has the potential to one day aid in diagnosis or treatment individualization.

Lastly, this complexity in the mechanisms must be reflected in the frameworks of diagnostics and therapy. Relying just on acid-suppressing medication does not solve problems with non-acid reflux, motility, or inflammatory damage, as Bertin et al. (2025) highlighted. A more accurate GERD phenotype may be achieved by combining impedance-pH monitoring, mucosal impedance, and biomarker evaluation; this allows for more personalized therapy (Argüero & Sifrim, 2024). The only way to achieve long-term symptom relief and mucosal repair is with a multimodal strategy that includes pharmaceutical, surgical, and lifestyle modifications.

CONCLUSION

The complex interplay of the mechanical failures, biochemical pollutants, neurogenic inflammatory metabolic effects, and microbial imbalances is the true cause of gastroesophageal reflux disease (GERD), as this comprehensive analysis has shown. A layered illness model needing mechanistic-specific therapeutic techniques is reflected in the combination of functional and structural alterations, such as the relaxation of the lower esophageal sphincter, mucosal damage mediated by bile and pepsin, cytokine activity, and sensory hypersensitivity.

This review emphasizes the need for multimodal diagnostic methods including impedance-pH monitoring, mucosal biomarkers, and motility tests, and it notes that acid-suppressive medications are inadequate for many subtypes of GERD. Personalized therapy options are necessary due to the recognition of obesity, post-bariatric anatomical change, hormonal changes, and microbial modifications as key causes. Improving GERD treatment outcomes will need future research to shift toward personalized phenotyping and targeted therapies.

LIMITATIONS

Despite the thorough mechanistic insights provided by this research, it is important to note that there are a number of limitations. Firstly, meta-analytic synthesis was not possible due to the included research' diverse diagnostic criteria, methodology, and measurement instruments. Second, there may have been non-English research that were relevant to the evaluation since they were not included in the database. Thirdly, several studies relied on small samples or did not have longitudinal follow-up, which limited the ability to draw causal conclusions, even if they were all peer-reviewed. Lastly, microbiome and genetic factors are two growing areas that need more rigorous data since they are yet under-investigated.

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